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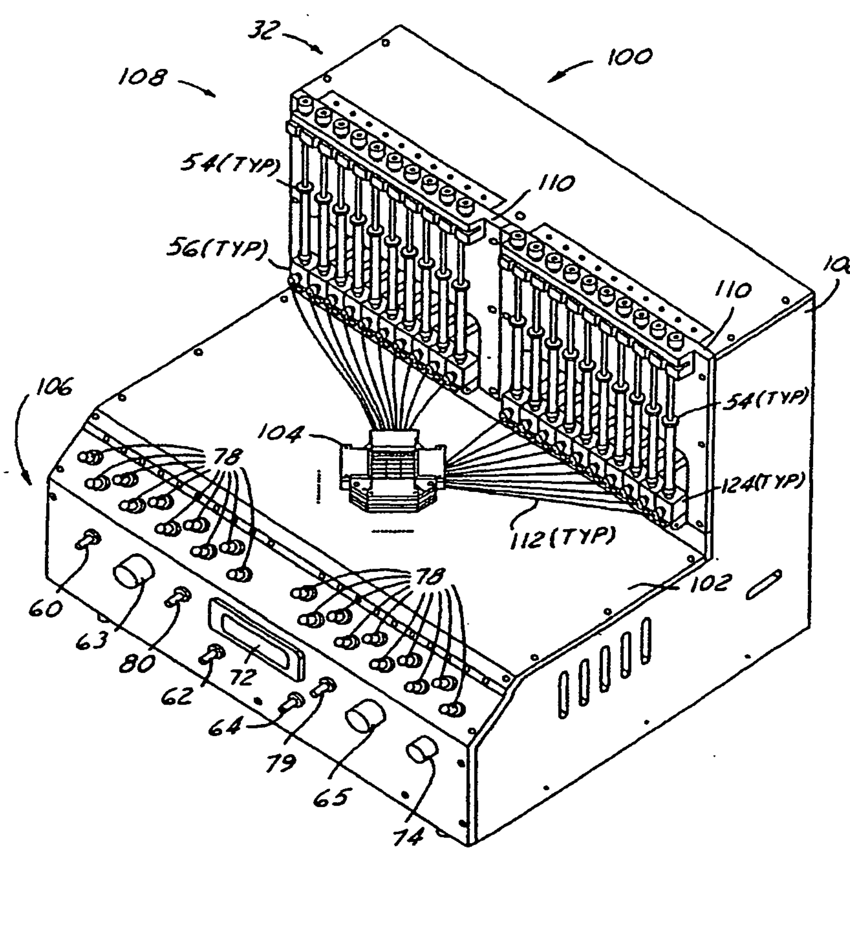
(54) Title: MICROFLUIDIC DEVICE INTERFACE



(57) Abstract: A microfluidic device interface (32) for a microfluidic device (12) has a work surface (102) and a microfluidic mounting device assembly (104) coupled to the work surface (102). A plurality of fluid sources (54) are provided having various reagents therein. A manifold (274, 276, 278, 280) fluidically couples the microfluidic device (12) to the fluid sources (54). A plurality of valves (56) are fluidly coupled to a respective fluid source (54) for controlling a fluid flow to the microfluidic device (12).

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MICROFLUIDIC DEVICE INTERFACE

Related Applications

The present invention claims priority to provisional application serial number 60/140, 095 filed June 19, 1999.

Technical Field

The present invention relates to microfluidic devices, and more particularly, to an apparatus for controlling the fluid flow from fluid sources to the microfluidic device.

Background Of The Invention

Methods of making a homologous series of compounds, or the testing of new potential drug compounds comprising a series of light compounds, has been a slow process because each member of a series or each potential drug must be made individually and tested individually. For example, a plurality of potential drug compounds that differ perhaps only by a single amino acid or nucleotide base, or a different sequence of amino acids or nucleotides are tested by an agent to determine their potential for being suitable drug candidates.

The processes described above have been improved by microfluidic chips which are able to separate materials in a microchannel and move the materials through the microchannel. Moving the materials through microchannels is possible by pressure pumping or by the use of various electro-kinetic processes such as electrophoresis or electro-osmosis. Fluids may be propelled through various small channels by the forces. For electro-osmotic forces, the forces are built up in the channel via surface charge buildup by means of an external voltage that can repel fluid and cause flow. For pressure pumping, low pressures are utilized to control the flow of fluids, break capillary barriers upon demand, and exhaust liquids from wells.

In fluid delivery in microfluidic structures, the device can consist of several layers. Channels often extend between the various layers. A capillary break structure is used in place of a valve downstream of an electrohydrodynamic pump in a channel. The capillary break is a location where the small channel ends abruptly as the entrance to a larger space. Capillary forces pull the fluid up to the end of the small cross-section channel but not beyond. This stops the fluid flow until additional pressure is provided. Prior to pushing fluid beyond the capillary break, a gap or discontinuity occurs in the fluid path immediately downstream of the capillary break. This prevents cross-contamination from other fluid paths.

Size, uniformity, and other fabrication tolerances may cause variances in the effectiveness of electrohydrodynamic pumps. Also, the microfluidic chip is preferably designed to be used with several different types of fluids. The variation of fluid properties, such as composition and temperature, also affect the ability of an electrohydrodynamic pump to overcome the capillary break.

Many of the chips proposed are to be automatically loaded with reagents through the use of a robotic device. Such a loading apparatus is relatively expensive. Manual loading is also done, however, this method is relatively expensive and is subject to human error.

It would, therefore, be desirable to control fluid distribution to and within a microfluidic chip in a reliable and convenient manner.

Summary Of The Invention

It is, therefore, one object of the invention to provide an improved fluid delivery mechanism to an array of reaction wells. It is a further object of the invention to reliably deliver fluid in a convenient compact manner.

In one aspect of the invention, a microfluidic device interface for a microfluidic device has a work surface and a microfluidic mounting device assembly coupled to the work surface. A plurality of fluid sources are provided having various regents therein. A manifold fluidically couples the microfluidic device to the fluid sources. The plurality of valves are fluidically coupled to a respective fluid source for controlling a fluid flow to the microfluidic device.

In a further aspect of the invention, microfluidic device interface for a microfluidic device includes housing having a work surface. A reagent support fixture has a plurality of legs extending from the work surface and a frame surface spaced apart from the work surface by the legs. The reagent support fixture has a microfluidic mounting device assembly and a plurality of manifolds coupled to the frame surface. A plurality of fluid sources is coupled to the manifolds. A plurality of valves fluidically couple a respective fluid source to the microfluidic device for controlling a fluid flow to the microfluidic device.

In yet another aspect of the invention, a method of coupling fluid to a microfluidic device comprises the steps of:

coupling a microfluidic device to a fluid source through a valve in a fluid line;

coupling a pressure source to the fluid source; and

operating the valve to provide a predetermined amount of fluid to the microfluidic device.

One advantage of the invention is that a convenient manner in which to load microfluidic chip is provided. The interface device can be substantially automated to load reagents at predetermined times.

Other objects and features of the present invention will become apparent when viewed in light of the detailed description of the preferred embodiment when taken in conjunction with the attached drawings and appended claims.

Brief Description of the Drawings

FIGURE 1 is perspective view of a microfluidic device which can be utilized in accordance with the present invention.

FIGURE 2 is an exploded perspective view of the microfluidic device of Figure 1.

FIGURE 3 is a block diagram of a fluidic and gas delivery system according to the present invention.

FIGURE 4 is an electrical block diagram of an interface device for use with the present invention.

FIGURE 5 is a computer interface block diagram for use with the present invention.

FIGURE 6 is a perspective of view of one implementation of a microfluidic interface device according to the present invention.

FIGURE 7 is a perspective view of an implementation of a fluid holding device shaped as a syringe.

FIGURE 8 is a perspective view of a pivot block which can be used with the present invention.

FIGURE 9 is a perspective view of a cassette mounting system which can be used with the present invention.

FIGURE 10 is a perspective view of a clamp plate block which can be used with the present invention.

FIGURES 11A and 11B are top and bottom views respectively of a discharge plate which can be used with the present invention.

FIGURE 12 is a perspective view of an off-station chip alignment system which can be used in accordance with the present invention.

FIGURE 13 is a perspective view of a top manifold which can be used with the present invention.

FIGURE 14 is a perspective view of an alternative embodiment of a microfluidic interface device.

FIGURE 15 is a perspective view of an alternate embodiment of a microfluidic interface device which can be utilized in accordance with the present invention.

FIGURE 16 is a view of the device shown in FIGURE 15 with a cover on it.

FIGURE 17 is a side cross-sectional view of the alternative microfluidic device according to the present invention.

FIGURE 18A is an exploded perspective view of an alternative microfluidic mounting device assembly which can be utilized in accordance with the present invention.

FIGURE 18B is a cross-sectional view of the frame member shown in FIGURE 18A, the cross-section being taken along line 18B-18B.

FIGURE 19 is a side view of the lowermost component of the microfluidic device shown in FIGURE 18.

FIGURE 20 is a side view of vacuum manifold for use with the device shown in FIGURE 15.

FIGURE 21 is a cross-sectional view of the manifold shown in of FIGURE 20, the cross-section being taken along line 20-20.

FIGURE 22 is a side view of a liquid supply manifold for use with the device shown in FIGURE 15.

FIGURE 23 is a cross-sectional view of the manifold shown in FIGURE 22, the cross-section being taken along line 23-23.

FIGURE 24 is a cutaway view of the liquid supply manifold shown in FIGURE 22.

FIGURE 25 is a partial cross-sectional view of a liquid supply manifold having a vial and valve assembly attached thereto.

FIGURE 26 is a key-slot holder member for the manifold shown in Figures 22, 23, 24 and 25.

Detailed Description of the Preferred Embodiment

Referring to Figures 1 and 2, a microfluidic distribution system 10 is shown incorporated into a microfluidic device 12. Fluid distribution system 10 has fluid inputs such as row reservoirs 16 and column reservoirs 17 coupled to a fluid source (not shown). Reservoirs 16, 17 are coupled to a main channel 18. Main channel 18 has a plurality of branches 20 extending therefrom.

Main channel 18 is coupled to a fluid source (not shown) that directs fluid outside of microfluidic device 12, which has not been diverted by one of the plurality of branches 20. The fluid source is preferably a pressurized

fluid source that provides pressurized fluid to main channel 18. A preferring embodiment type of a pressurized fluid source will be described below.

Microfluidic device 12 is preferably comprised of a plurality of adjacent layers. In the present example, a top layer 22, a second layer 24, a seal layer 26 and a well layer 28 are used. The composition of each layer may, for example, be glass, silicon, or another suitable material known to those in the art. Each layer may be bonded or glued together in a manner known to those skilled in the art. For example, the layers may be anodically bonded.

Second layer 24 is illustrated as single layer. However, second layer 24 may be comprised of several layers interconnected through fluid channels. Although only one seal layer 26 is shown for simplicity, one skilled in the art would recognize that a seal layer may be used between any of the layers.

Branches 20 provide interconnections to wells 29 of well layer 28 through the various layers 22 through 26. The various openings and channels forming branches 20 may be formed in a conventional manner, such as by etching or drilling. Drilling may be accomplished by laser drilling.

Main channel 18 in the preferred embodiment is formed by first layer 22 and second layer 24. Interlayer feed channel 30, as illustrated, is conical in shape. However, interlayer feed channel 30 may also be cylindrical in shape.

The microfluidic device 12 has row fluid outputs 31 and column fluid outputs 33. As will further be described below, a vacuum may be coupled to outputs 31, 33 to extract excess fluid not delivered to reaction wells within chip 12.

Referring now to Figure 3, a block diagram of a microfluidic device interface 32 is illustrated. Generally, this system operates by controlling an amount of gas to displace fluid from a fluid source into the microfluidic chip. More specifically, a gas source 34 is coupled to a low-pressure regulator 36 and a high-pressure regulator 38. The regulators 36, 38 are coupled to a low pressure input line 40 and a high pressure input line 42, respectively. The low pressure input 40 and the high pressure input line 42 are coupled to a channel input 44 through a respective low pressure valve 46 and a high pressure valve 48. A low-pressure sensor 50 and a high pressure 52 are coupled to the low pressure input line 40 and high pressure input line 42, respectively. Channel input 44 couples low pressure input line 40 and high pressure input line 42 to each channel of microfluidic device interface 32. In the present example, 20 parallel channels 53 are provided, only the first of which and the last of which are illustrated for simplicity. Each channel 53 has a reagent (fluid) source 54 such as a reagent syringe or vial and a control valve 56. In the present example, twenty (20) reagent sources 54 and twenty (20) control valves 56 are used, one for each channel 53. Each control valve 56 is coupled to a chip interface cassette 58 which is used to couple fluid from reagent source 54 to the microfluidic device.

In the present example, low-pressure regulator 36 may be set between zero and one PSI. High-pressure regulator 52 may be adjusted between zero and 30 PSI. The number of reagent sources 54 was chosen to correspond to a microfluidic chip having 10 rows and 10 columns. Thus, each one of the reagent sources 54 corresponds to either one row or one column.

Pressure sensors 50, 52 may be calibrated to ensure the proper readings. Two convenient manners in which the pressure sensors 50, 52 may be calibrated include using a precision voltage divider circuit so that the output of the sensors is accurately scaled and using the displayed value and manually

converting the display value using a lookup table. Either method may be employed by microfluidic device interface 32.

A controller 60 may be coupled to microfluidic device interface 32 to partially or fully automate the system. Controller 60 is preferably microprocessor-based and may operate with some software control.

In operation, gas source 34 provides a source of gas that is used for displacing the fluid from reagent source 54 to the microfluidic device. Gas source 34 may, for example, be a nitrogen gas source. The valves 46 and 48 are selectively operated to provide low pressure or high pressure to reagent sources 54. Typically, low pressure is provided when the microfluidic chip is initially loaded. To overcome capillary breaks within the microfluidic chip, a higher pressure may be required. In the preferred embodiment, either low-pressure line 40 or high-pressure line 42 is coupled to reagent source 54 through channel input 44. Of course, those skilled in the art would recognize both could be coupled simultaneously in an additive manner. The amount and timing of the fluid from each reagent source 54 is controlled by its respective control valve 56. Each channel 53 has its associated control valve 56 coupled to a row or column of the microfluidic device. Any mixing of the individual reagents in each reagent source 54 takes place on-board the microfluidic device.

Initially, valve 46 is open while valve 48 is closed. Low pressure is then provided to channel input 44. When desired, the valves 46 are opened for a pre-determined amount of time and thus, fluid is coupled to the interface cassette 58. As will be evident below, control valves 56 may be simultaneously operated to simultaneously deliver fluid to interface cassette 58. Although interface cassette 58 is illustrated as a single box, the fluid lines from the control valves 56 to interface cassette 58 are preferably a plurality of individual lines.

One advantage of the fluid delivery system is that the control valves are in the fluid path rather than in the gas path. This allows more

accurate control of fluid delivery than gas path control in part due to the lesser compressibility of liquid versus gas.

Referring now to Figure 4, an electrical block diagram of microfluidic device interface 32 is shown. Common elements to those shown in Figure 3 use the identical reference numeral. A pressure selector switch 60 may be used to choose whether a high pressure or a low pressure is desired. Pressure selector switch may be implemented as a pair of toggle switches that enable either high pressure or low pressure. Upon the activation of low pressure, low-pressure control 62 may be used to select the desired low pressure. A high-pressure control 64 is coupled to high-pressure regulator 38 to select the desired high pressure. Both low-pressure control 62 and high-pressure control 64 may be implemented in an adjustable dial.

The system may be powered by a five volt power supply 66, a 12 volt power supply 68 and a 24 volt power supply 70 to accommodate the various components that may used various voltage sources. Microfluidic device interface 32 may have a display 72 and a display selector switch 74. Display selector switch 74 may be used to select the information to be displayed on digital display 72.

Control valves 56 may be coupled to a solid state relay interface board 76 or other similar device for electrically coupling control valve 56 and selection switch 78. Interface board 76 couples a selection switch 78 to control each control valve 56 for each channel. One selection switch 78 is provided for each control valve 56. In the present example, selection switches 78 are formed of a three-position toggle switch. The three positions of the selection switch 78 are pause, off, and momentary.

A master pulse selector switch 80 may be coupled to each selection switch 78 or directly to interface board 76 to simultaneously control a pulse to each control valve 56. Master pulse selector switch 80 may be coupled

to a pulse generator 82. The pulse generator 82 may be located within microfluidic device interface or as an external function generator. Pulse generator 82 provides the actual electrical pulse that will interface to each control valve 56.

Referring now to Figure 5, a block diagram of a more automated microfluidic interface 32 is shown. Common elements to Figures 3 and 4 are labeled with identical reference numerals. A host computer 84 is used to control the operation of microfluidic interface 32'. Host computer may, for example, have a plurality of digital input/output (I/O) lines 86, an analog digital converter 88 and a digital to analog converter 90. Digital I/O lines 86 may be directly coupled to selection switches 78. However, in a preferred embodiment, a pulse enable and generation circuit 92 may be used to enable and generate pulses for selection switches 78. Analog digital converter 88 is coupled to pressure sensors 50, 52 to convert the usually analog outputs of pressure sensors 50, 52 to a digital signal may be used for calculations and display within host computer 84.

Digital to analog converter 90 is coupled to pressure regulators 36, 38. Digital to analog converter 90 converts the desired pressure regulator setting from host computer 84 and converts it to analog by which pressure regulators 36, 38 are controlled.

Host computer 84 is microprocessor-based and is run by software for sequencing gas pressure and fluid deliveries. In a constructed embodiment, LabView (TM) by National Instruments provides a suitable software package for controlling computer 84. Host computer 84 may provide many other control functions such as effluent vacuum monitoring, back end vacuum control, internal pulse width generation, multiple simultaneous selection of low pressure, high pressure or vacuum for individual reagent delivery lines and temperature control of an external source.

Referring now to Figure 6, a physical implementation of a first embodiment of the microfluidic device interface 32 is shown. Microfluidic device interface 32 incorporates many of the same features as shown in Figures 3 and 4 above. Microfluidic device interface 32 has a housing 100 that is used to interconnect the various control wires and gas pressure lines as described above. Housing 100 has a work surface 102 that is used to support a microfluidic mounting device assembly 104. In a preferred embodiment, work surface 102 may be formed of metal and coated with a Teflon™ coating to prevent the reagents from sticking to the work surface 102.

Housing 100 also has a control panel 106 that has each of the activation switches described above. Control panel 106 may also have digital display 72 therein. The switches that are incorporated into control panel 106 include high pressure control 64, high pressure selector 65, low pressure control 62, low pressure selector 63, pressure selector switch 60, display selector switch 74, master pulse selector switch 80 and channel selection switches 78. A manual/automated control switch may also be incorporated into control panel 106 to allow either manual or computer control selectability.

Housing 100 has a reagent support portion 108. As illustrated, reagent support portion supports 20 reagent sources into support fixtures 110. Each reagent source 54 may store different reagents. Associated with each reagent source 54 is a pivot block 124 having control valve 56 therein. Control valves 56 are coupled to microfluidic mounting device assembly 104 through fluidic lines 112. Fluid lines 112 may be flexible hoses for convenience.

As will be further described below, support fixture 110 is preferably configured so that reagents may be loaded into reagent sources 54 and may be conveniently loaded and removed.

Referring now to Figure 7, a suitable configuration for a reagent source 54 is illustrated. Reagent source 54 is configured as a syringe 114. Syringe 114 has a plunger 116 that is received within a cylinder 118. Although various types of reagent sources 54 may be employed, syringe 114 has the advantage of being easy to transport as well as to load fluid into the cylinder portion 118 by drawing plunger 116 from a position fully within cylinder outward. Fluid is then drawn into cylinder 118 through end seal hole 120. Plunger 116 has end seal hole 120 extending therethrough. Hole 120 will eventually be coupled to a gas pressure source so that fluid may be displaced from within cylinder 118. In a commercial embodiment, reagent sources 54 may be distributed prepackaged with reagents suitable for a particular application.

Referring now to Figure 8, a perspective view of a pivot block 124 is shown. Pivot block 124 has a pivot coupling 126 that is used to pivotally couple syringe 114 into support fixture 110. Pivot coupling 126 has a receiving hole 128 for receiving end 120 of syringe 114. Pivot block 124 also has a valve hole 130 that may be used to control the movement of fluid from syringe 114 through pivot block 124. Pivot block 124 has a fluid outlet 132 that is used to couple fluid from within syringe 114 to the microfluidic device assembly 104. The control valve may be a solenoid operated control valve or other valve suitable to be received within valve hole 130.

Referring now to Figure 9, a perspective view of microfluidic mounting device assembly 104 is shown coupled to work surface 102. Cassette mounting device assembly 104 has a mounting flange 134 and an adapter plate 136. Mounting flange 134 is used to couple adapter plate 136 to work surface 102. Clamps 138 are used to secure a chip and interface assembly plate 140.

Chip and interface assembly 140 has a microfluidic chip 142 housed between a clamp plate interface 144 and a discharge plate 146. Locating

pin 148 may be located at various locations on adapter plate 136 to properly position the clamp and interface assembly. The mechanical configuration of clamp plate 144 and discharge plate 146 are further described below.

In operation of microfluidic device interface, microfluidic mounting device assembly 104 securely positions the chip and interface assembly 140 during fluid distribution from the reagent sources 54.

Referring now to Figure 10, a perspective view of a clamp plate interface 144 is illustrated. Clamp plate interface 144 has a plurality of row through holes 150 and a plurality of column through holes 152 that correspond with the input holes in a microfluidic chip. As would be evident to those skilled in the art, the exact configuration should align with the configuration of the microfluidic chip. In the present example, 10 column input holes 152 and 20 row input holes 150 are illustrated. Only 10 row input holes would likely be used at a particular time. Clamp plate interface 144 has row output holes 154 that correspond with the output holes on the microfluidic chip. Any excess fluid input through row input holes 150 may be removed through row output holes 154. Clamp plate interface 144 also has column output holes 156 that correspond with the output holes on the microfluidic chip. Preferably, each column within the microfluidic chip has an input hole 52 and an output hole 156.

Clamp plate interface 144 may also include a locating holes 158 that correspond with the locating pins 148 shown in Figure 9 above. Clamp plate interface 144 may also have a clamp support structure 160 that is used to assist the holding of microfluidic chip 142 in a stationary position during testing. Clamp plate interface 144 may also have manifold locating holes 162 located thereon. Manifold locating holes 162 may be used to locate a fluid manifold during assembly as will be further described below.

Referring now to Figures 11A and 11B, a perspective view of discharge plate 146 is shown. In Figure 11A, top surface 164 of discharge plate 146 is illustrated. In Figure 11B, bottom surface 166 of discharge plate 146 is illustrated. Discharge plate 146 is preferably configured similarly to that of clamp plate interface 144. The plurality of discharge through holes 168 may be used to align with the drain holes of a microfluidic chip. Discharge plate 146 is positioned adjacent the opposite surface of the microfluidic chip than clamp plate interface 144. A plurality of locating holes 170 positioned similar to that of locating holes 158 may be positioned around discharge plate 146. A plurality of holes 172 may be positioned around discharge plate 146 for locating various clamping devices and for location of discharge plate 146 upon adapter plate 136. A support structure 174 may also be included within the center of discharge plate 146 for supporting a microfluidic chip. A recess 176 may be included around the discharge holes 168 on bottom surface 166 as is best shown in Figure 11B.

Referring now to Figure 12, it is important that the clamp plate interface 144 and discharge plate 146 are properly aligned with each other to allow fluid to be coupled therethrough. An off-station chip alignment device 180 may be used to provide alignment. An X axis positioner 182 and a Y axis positioner 184 may be employed. X axis positioner 182 and Y axis positioner 184 may each be configured as a micrometer. X axis positioner 182 and Y axis positioner 184 have an adjustment knob 186 that may be used to both coarsely and finely adjust the discharge plate 146, clamp plate 144, and microfluidic chip 142 with respect to each other.

A Z axis positioner 188 may also be included in off station alignment device 180. Z axis positioner 188 may be used to adjust microfluidic chip 142, clamp plate interface 144 and discharge plate 146 in a vertical direction. Z axis positioner 188 may also be configured in a micrometer form having an adjustment knob 190.

Referring now to Figure 13, a top manifold 200 is illustrated. Top manifold 200 is used to locate the fluid lines 112 (best shown in Figure 6). In the preferred embodiment, two separate manifolds being the mirror image of each other are provided. Top manifold 200 has row input holes 202 and column input holes 204. Top manifold 200 further has fluid line channels 206 that are used to securely fasten the fluid lines 112 of Figure 6 therein. The ends of the fluid lines 112 are received within row input holes 202 and column input holes 204. Top manifold 200 may also include locating holes 208 that align with the locating pins 148 shown in Figure 6. Locating holes 208 align with locating holes 170 and 158 as shown above. A clamp plate 210 may be securely coupled to top manifold 200 to hold the fluid lines within fluid line channels 206.

Referring now to Figure 14, block diagram for an alternative embodiment of a microfluidic device interface 220 is generally shown. In this embodiment, a computer assembly rack 222 is incorporated into the housing of the microfluidic device interface 220 as will be shown below. Microfluidic device interface 220 includes channel control valves 224, pressure control valves 226, pressure regulators 228, pressure sensors 230, temperature sensors 232 and a heater element 234. The configuration is similar to that described above in Figures 4 and 5 with more automated control.

A plurality of terminal blocks 236 may be incorporated into microfluidic device interface 220 to electrically connect control valves 224, pressure regulators 228, pressure sensors 230, temperature sensors 232 and heater element 234 to computer assembly rack 222.

Microfluidic device interface 220 may also include a channel control 238, indicators 240 and temperature setting control 242, each of which may be coupled to computer assembly rack 222 through terminal block 236. Channel control 238 may be used to control the operation of each channel. For example, the channel control 238 may be used to control whether a single pulse

is used and the pressure settings of each channel. Indicators 240 include a pressure indicator, LED indicators for various other functions and a temperature indicator. Temperature setting control 242 may include a control for setting the temperature set point 242. Channel control 238, indicators 240 and temperature set point 242 may include on-screen visual indicators. The control may, for example, be menu-driven.

Computer assembly rack 222 includes a high voltage isolated input/output (I/O) card 244, an analog to digital conversion card 246, a CPU card 248, power supply 250, a hard drive 252 and a floppy drive 254. A plurality of empty slots may be left in computer assembly rack 222 for future expansion.

CPU card 248 may also be coupled to external devices such as, but not limited to, a CD ROM drive 258, a video display 260, keyboard and mouse 262 and a network 264. These devices may be included as part of microfluidic device interface 220. However, these devices are likely to be separate external components in a commercial embodiment. These devices may be used to further process, record and store data gathered.

Keyboard and mouse 262 may be used to control channel control 238, indicators 240 and temperature setting control 242 through a software program such as LabView™ as described above. The general operation of microfluidic device interface 220 is similar to that described above with respect to microfluidic device interface 220.

Referring now to Figure 15, in this embodiment, a housing 266 may be used to house essentially all of the devices described above with respect to Figure 14. Housing 266 includes a work surface 268. Work surface 268 supports a reagent support fixture 270. Reagent support fixture 270 includes a microfluidic mounting device assembly 272. One advantage of the present embodiment is that the reagents in reagent support fixture 270 are brought

closer to microfluidic mounting device assembly 272 and thus are easier to control and require less priming of the fluidic path upon startup. Reducing priming is important in applications in which the reagents are expensive.

Reagent support fixture 270 includes a row vial manifold 274 and a column vial manifold 276. Reagent support fixture 270 also includes a row vacuum manifold 278 and a column vacuum manifold 280. Reagent support fixture 270 supports row vial manifold 274, column vial manifold 276, row vacuum manifold 278 and colymn vacuum manifold 280 are mounted on a frame surface 282. Frame surface 282 is held a distance from work surface 268 by legs 284. Preferably, frame surface 282 is square or rectangular in shape so that each side supports one of manifolds 274, 276, 278, 280. Each manifold is used to control the inputs to microfluidic mounting device assembly 272. Each channel, as described above, may be individually controlled through valves 286. Valves 286 are preferably each individually electrically operated by solenoids. Row vial manifold 274 and column vial manifold 276 are coupled to reagent vials 288 which are supported under row vial manifold 274 and column vial manifold 276 as will be further described below. A plurality of tube fittings 290 may also be incorporated into each manifold 274, 276, 278, 280. Tube fittings 290 are used to couple connection tubes 290 from the manifolds to the microfluidic mounting device assembly 272.

Legs 284 are preferably hollow and align with openings in work surface 268 so that the control wires and pressure tubes (not shown) within housing 266 may be coupled through legs 284 in a neat and convenient manner.

Referring now to Figure 16, a cover 292 may be used over reagent support fixture 270 in an operating environment. Cover 292 may be made of plastic or metal and used to protect microfluidic mounting device assembly 272 and in particular the fluid interconnection lines.

Referring now to Figure 17, a cross-sectional view of microfluidic device interface 220 is generally shown. Beneath work surface 268, a camera 294 may be mounted. Camera 294 may be positioned beneath an opening 296 in work surface 268. The camera is an optional device and may also be mounted above reagent support fixture 270 outside of housing 266.

Referring now to Figures 18A, 18B and 19, an exploded view (Figure 18A) of a microfluidic mounting device assembly 272 includes a cassette assembly 300 that includes a holder bottom 302, a microfluidic cassette or chip device 304 and a holder top 306. Microfluidic device 304 may be one of several microfluidic device configurations. However, the specific configuration of microfluidic mounting device assembly 272 may be tailored for the individual device configuration. Holder bottom 302 has extensions 308 that extend upward from a base 310. Extensions 308 are also generally L-shaped to provide a high tolerance fit for microfluidic device 304. Microfluidic device 304 preferably extends between extensions 308 in a secure manner. Extensions 308 are used to ultimately locate microfluidic device assembly 304 within microfluidic mounting device assembly 272.

Base 310 may also include light channels 312 that may be used to house light sources (not shown) for illuminating microfluidic device 304. Base 310 may also include heating strips 314 coupled to the bottom thereof. Heating strips 314 may be coupled to CPU card 248 for control. One or more temperature sensors 316 may also be coupled to base 310 which provide so temperature feedback to the CPU.

Extensions 308 may also include mounting holes 318 that are used to assemble the microfluidic mounting device assembly 272. Extensions 308 may also include cassette mounting hole 320 for assembling the cassette 300.

Holder top 306 is preferably sized similarly to that of holder bottom 302. Holder top 306 has an insert opening 322, along with mounting holes 324 that extend therethrough and align with mounting holes 318 on holder bottom 302. Holder top 306 may also have cassette mounting holes 326 that have fasteners 328 therein. Fasteners 328 and mounting holes 326 align with cassette mounting holes 320 on holder bottom 302. Fasteners 328 are used to hold microfluidic device 304 in holder bottom 302. Fasteners 328 may be used to securely hold microfluidic device 304 so that sufficient pressure is applied between the layers of the device in order to compress and seal the various layers and prevent the device from leaking.

A frame insert 330 is generally rectangular in shape and is sized to fit within insert opening 322 of holder top 306. Insert 330 has plurality of row through holes 332 and column through holes 334.

Column through holes 334 and row through holes 332 align with the row openings and column openings on the top of microfluidic device 304. A plurality of extension tubes 338 may be mounted within each row through hole 332 and column through hole 334. As shown, frame insert 330 is rectangular having an opening 340 therein. However, insert 330 may also be a solid component without an opening.

As shown best in Figure 18B, a strip gasket 331 is preferably provided on the underside of frame insert member 330 around row through holes 332 and column through holes 334. Extension tubes 338 may also extend through insert to gasket 331.

Microfluidic mounting device assembly 272 may also include a top plate 342. Top plate 342 has row through holes 344 and column through holes 346. When assembled, extension tubes 338 preferably extend through row through holes 344 and column through holes 346 so that supply tubes 290 may be coupled thereto. Top plate 342 may have a top plate opening 348 which

aligns with opening 340 and 330. Although not shown, a clear block may be placed within top plate opening 348 so visual monitoring of the operation of microfluidic device 304 may be monitored. Top plate 342 may have mounting holes 350 mounted therethrough which align with the mounting holes of the other members of microfluidic mounting assembly 272. Although not illustrated, various gaskets and seals may be employed to prevent fluid leakage between various layers as would be evident to those skilled in the art.

One advantage of this embodiment over the previous embodiment is that if high tolerance is met in the various layers, the mounting holes and geometry of the pieces may be used for alignment.

Microfluidic mounting device assembly 272 may also include a pair of mounting plates 352 on each side of the assembly 272. Mounting plates 352 are coupled to top plate 342 through mounting holes 354. Fasteners 356 extend through the mounting holes of mounting plate 352, top plate 342, holder top 306 and holder bottom 302.

Blocks 360 are coupled to mounting plates 352 and they are used to mount microfluidic mounting device assembly 272 to work surface 268 (shown above). Mounting blocks 360 are preferably formed of a phenolic or other temperature insulating material. A temperature insulating material is used to prevent work surface 268 from transferring heat from microfluidic mounting device assembly 272 to the housing 266 and through work surface 268.

Referring now to Figures 20 and 21, a manifold 362 that may be used for row vacuum manifold 278 and column vacuum manifold 280 is illustrated. Manifold 362 has vacuum in openings 364 and vacuum out openings 366 that are coupled to a central channel 358. Manifold 362 has inputs 370 that are coupled to the microfluidic device, as well as outputs 372 that are coupled to a vacuum source 374. In an actual implementation, the vacuum source 374 may be located within the housing of the microfluidic

device interface. Vacuum source 374 may also include a filter to catch fluids therein. An electrically operated valve 376 may be coupled between inputs 370 and outputs 372 to control the application of a vacuum to the microfluidic device. Valve 376 has control wires 377 extending therefrom to electrically control valve therethrough. If the rows and columns are varied from different microfluidic designs, then the number of inputs 370 and outputs 372 may vary accordingly.

Referring now to Figures 22, 23 and 24, a vial manifold 380 is illustrated. Vial manifold 380 may be either a column vial manifold 376 or row vial manifold 374 as described above. Vial manifold has a pressure input line 382 and a pressure output line 384. Pressure input line 382 may, for example, be coupled to a high-pressure source or a low pressure as described above. Pressure input 382 and pressure output 384 are coupled to a central channel 386. Vial manifold 380 is coupled to a pressure input 388 that is coupled to the high pressure or low pressure or sources. Vial manifold 380 is also coupled to a pressure output 388. Pressure output 388 and pressure input 390 are coupled together by a valve 392, which, for example, may be operated by solenoid 386. Pressure output 388 acts as a fluid output for the microfluidic device. Fluid is coupled to a connector 391 that couples a fluid line 393 to the microfluidic device. Manifold also includes a vial mount 394 for each channel of the microfluidic device.

Referring now to Figure 25, vial mount 394 is shown in more detail. Vial mount 394 is used to mount a glass vial 288 as shown above into a recess 396. Vial 288 has a lip 398 that is received in recess 396. A seal, such as O-ring 400, is placed between lip 398 and recess 396 to provide a sufficient seal to draw fluid from within vial.

Vial 288 has a fluid reservoir 402 that preferably has a cone-shaped bottom 404. A withdrawing tube 406 extends from valve 392 into the

fluid reservoir 402 and preferably close to the bottom of cone-shaped bottom 404. Drawing tube 406 extends through an opening 408 in the top of vial 288. Opening 408 is used to provide fluid or pressure input from central channel 386 around withdrawing tube 406. This allows fluid to be withdrawn in a compact manner.

Referring now to Figure 26, a locking member 410 is illustrated having a plurality of key-hole shaped openings 412. Openings 412 have a large portion 414 and a small portion 416. Locking member 410 mounts within vial manifold 380 so that vials may be inserted within larger portion 414. The smaller portion 416 locks the vials into place when the member 410 is moved laterally relative to manifold 380.

While particular embodiments of the invention have been shown and described, numerous variations and alternate embodiments will occur to those skilled in the art. Accordingly, it is intended that the invention be limited only in terms of the appended claims.

What is claimed is:

1. A microfluidic device interface for a microfluidic device comprising:

a work surface;

a microfluidic mounting device assembly coupled to said work surface;

a plurality of fluid sources;

a manifold fluidically coupling the microfluidic device to said fluid sources; and

a plurality of valves fluidically coupled to a respective fluid source for controlling a fluid flow to a microfluidic device.

2. A microfluidic device interface as recited in claim 1 wherein said microfluidic device comprises a multi-layer fluidic device.

3. A microfluidic device interface as recited in claim 1 wherein said manifold comprises a plurality of fluid line channels.

4. A microfluidic device interface as recited in claim 1 wherein said mounting assembly comprises an adapter plate, a clamp plate interface and a discharge plate.

5. A microfluidic device interface as recited in claim 4 wherein said clamp plate comprises a plurality of through holes corresponding to fluid input holes of the microfluidic chip.

6. A microfluidic device interface as recited in claim 4 wherein said clamp plate comprises a plurality of through holes corresponding with fluid output holes of the microfluidic chip.

7. A microfluidic device interface as recited in claim 4 further comprising a clamp coupled to said adapter plate.

8. A microfluidic device interface as recited in claim 1 wherein said fluid sources comprise a reagent source.

9. A microfluidic device interface as recited in claim 8 wherein said reagent source comprises a syringe.

10. A microfluidic device interface as recited in claim 1 further comprising a chip alignment station comprising a plurality of positioners.

11. A microfluidic device interface as recited in claim 1 wherein said manifold comprises a first manifold, a second manifold, a third manifold and a fourth manifold positioned adjacent to a first side, a second side, a third side and a fourth side, respectively.

12. A microfluidic device interface as recited in claim 1 wherein said first manifold, a second manifold, a third manifold and a fourth manifold comprise the plurality of valves said plurality of valves corresponding to an input hole or an output hole of the microfluidic device.

13. A microfluidic device interface as recited in claim 1 wherein said microfluidic mounting device comprises a cassette assembly for receiving the microfluidic device.

14. A microfluidic device interface as recited in claim 13 wherein said cassette assembly comprises a holder bottom and a holder top sized to receive the microfluidic device therebetween.

15. A microfluidic device interface as recited in claim 14 wherein said holder top comprises an insert opening, said cassette assembly comprising an insert positioned within said insert opening.

16. A microfluidic device interface as recited in claim 15 wherein said insert comprises a plurality of through holes corresponding to a respective input hole or output hole of the microfluidic device.

17. A microfluidic device interface as recited in claim 16 wherein said through holes have a respective extension tube therein.

18. A fluid delivery system for a microfluidic chip having a plurality of fluid inputs and a plurality of column inputs comprising:

a gas pressure source;

a fluid source having fluid therein, said fluid source coupled to said gas pressure source; and

a valve coupled between said fluid source and said microfluidic chip for controlling a distribution of fluid to said microfluidic device.

19. A fluid delivery system as recited in claim 18 further comprising a valve control circuit coupled to the valve, said valve control circuit comprising a controller.

20. A fluid delivery system as recited in claim 18 comprising a pulse enable/generation circuit.

21. A fluid delivery system as recited in claim 1 further comprising an interface relay board coupled to said control valve.

22. A fluid delivery system as recited in claim 1 wherein said gas pressure source comprises a low pressure gas source.

23. A fluid delivery system as recited in claim 1 wherein said gas pressure source comprises a high pressure source.

24. A microfluidic processor for a microfluidic device comprising:

a housing said housing having a work surface and a fluid securing portion extending substantially perpendicular to said work surface;

said fluid support surface including a support fixture for securing fluid reservoirs;

a plurality of valves coupled to said support fixture;

a gas pressure source coupled to said fluid reservoirs for displacing fluid from said fluid reservoirs and into the microfluidic device; and,

a control panel coupled to said valves for controlling the operation of said valves.

25. A microfluidic processor as recited in claim 24 further comprising a controller coupled to said valves, said controller controlling a timing of opening and closing a valve.

26. A microfluidic processor as recited in claim 24 further comprising a plurality of selection switches coupled to each of said control valves.

27. A microfluidic processor as recited in claim 24 wherein said control panel further comprises a pressure selector switch.

28. A microfluidic processor as recited in claim 24 wherein said control panel further comprises a master pulse selector switch.

29. A microfluidic processor as recited in claim 24 wherein said control panel further comprises a digital display

30. A microfluidic processor as recited in claim 24 wherein said work surface has an opening therethrough and further comprising a camera directed at the microfluidic device.

31. A microfluidic device interface for a microfluidic device comprising:

a housing having a work surface;

a reagent support fixture having a plurality of legs extending from said work surface and a frame surface spaced apart from the work surface, said reagent support fixture having a microfluidic mounting device assembly and a plurality of manifolds coupled to the frame surface;

a plurality of fluid sources coupled to the manifolds; and

a plurality of valves fluidically coupling a respective fluid source to the microfluidic device for controlling a fluid flow thereto.

32. A microfluidic device interface as recited in claim 31 wherein said plurality of manifolds comprises a row vial manifold, a column vial manifold, a row vacuum manifold and a column vacuum manifold.

33. A microfluidic device interface as recited in claim 31 wherein said plurality of valves are extend from above the plurality of manifolds.

34. A microfluidic device interface as recited in claim 31 wherein said plurality of fluid sources extend below the plurality of manifolds.

35. A microfluidic device interface as recited in claim 31 wherein said valves are electrically actuated and have control wires coupled thereto.

36. A microfluidic device interface as recited in claim 35 wherein said legs are hollow, said control wires are at least partially positioned within said legs.

37. A microfluidic device interface as recited in claim 31 wherein said microfluidic mounting device assembly comprises a cassette assembly for receiving the microfluidic device.

38. A microfluidic device interface as recited in claim 37 wherein said cassette assembly comprises a holder bottom and a holder top sized to receive the microfluidic device therebetween.

39. A microfluidic device interface as recited in claim 38 wherein said holder top comprises an insert opening, said cassette assembly comprising an insert positioned within said insert opening.

40. A microfluidic device interface as recited in claim 39 wherein said insert comprises a plurality of through holes corresponding to a respective input hole or output hole of the microfluidic device.

41. A microfluidic device interface as recited in claim 40 wherein said through holes have a respective extension tube therein.

42. A microfluidic device interface as recited in claim 31 wherein said work surface has an opening therethrough and further comprising a camera directed at the microfluidic device.

43. A microfluidic device interface as recited in claim 31 further comprising a cover at least partially covering said reagent support fixture.

44. A method for coupling fluids to a microfluidic device comprising the steps of:

coupling a microfluidic device to a fluid source through a valve in a fluid line;

coupling a pressure source to the fluid source; and

operating the valve to provide a predetermined amount of fluid to the microfluidic device.

45. The method as recited in claim 44 wherein the microfluidic device comprises a multi-layer device.

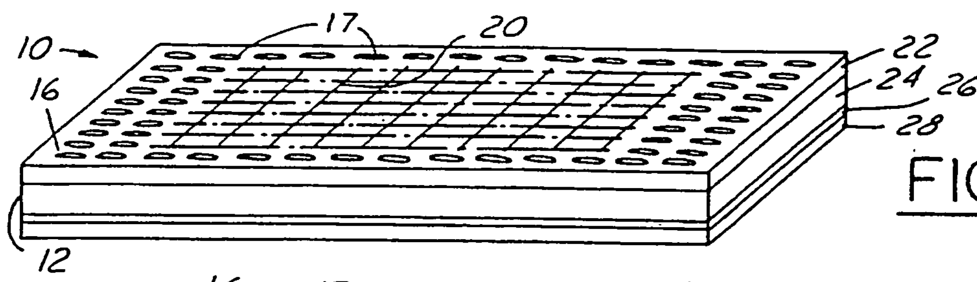


FIG. 1

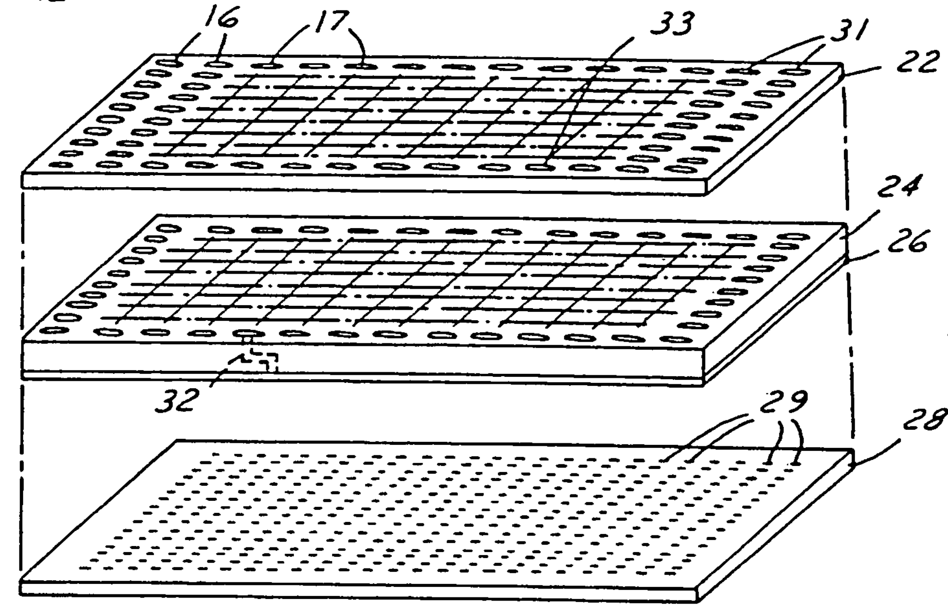


FIG. 2

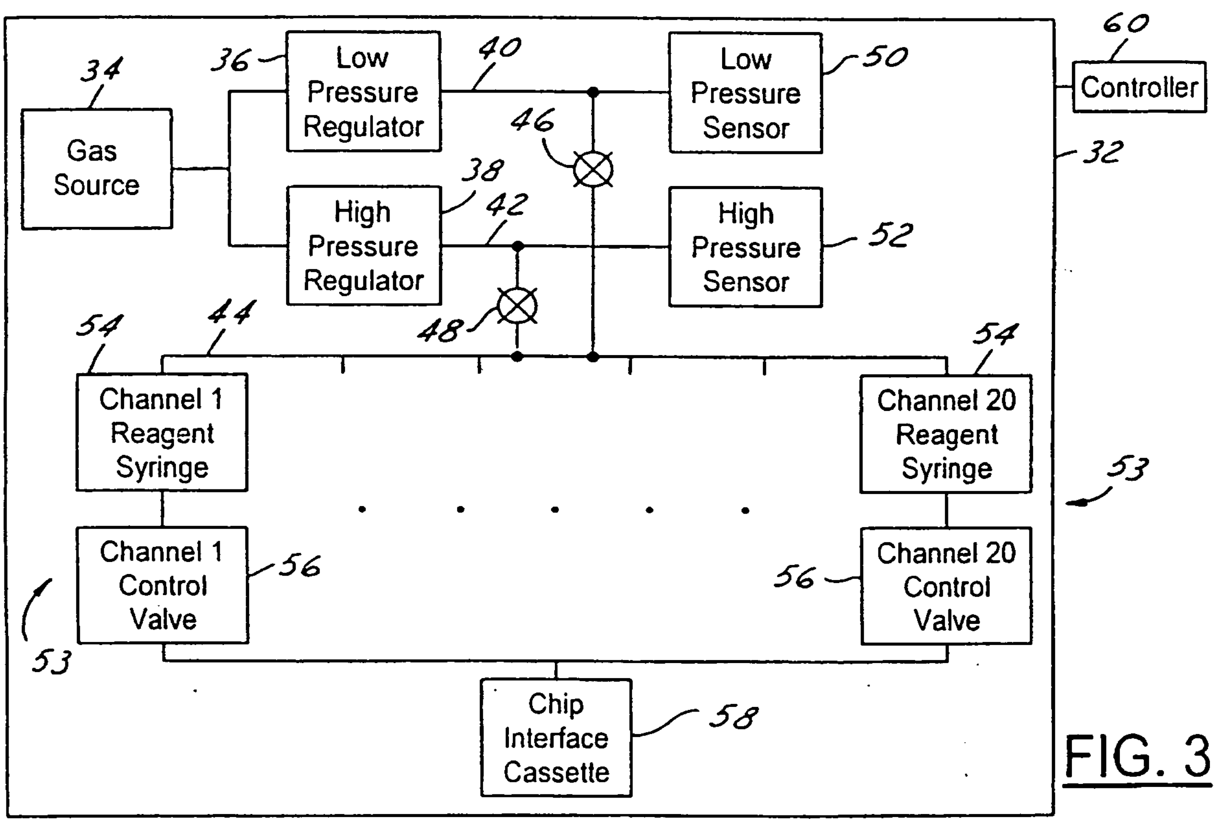
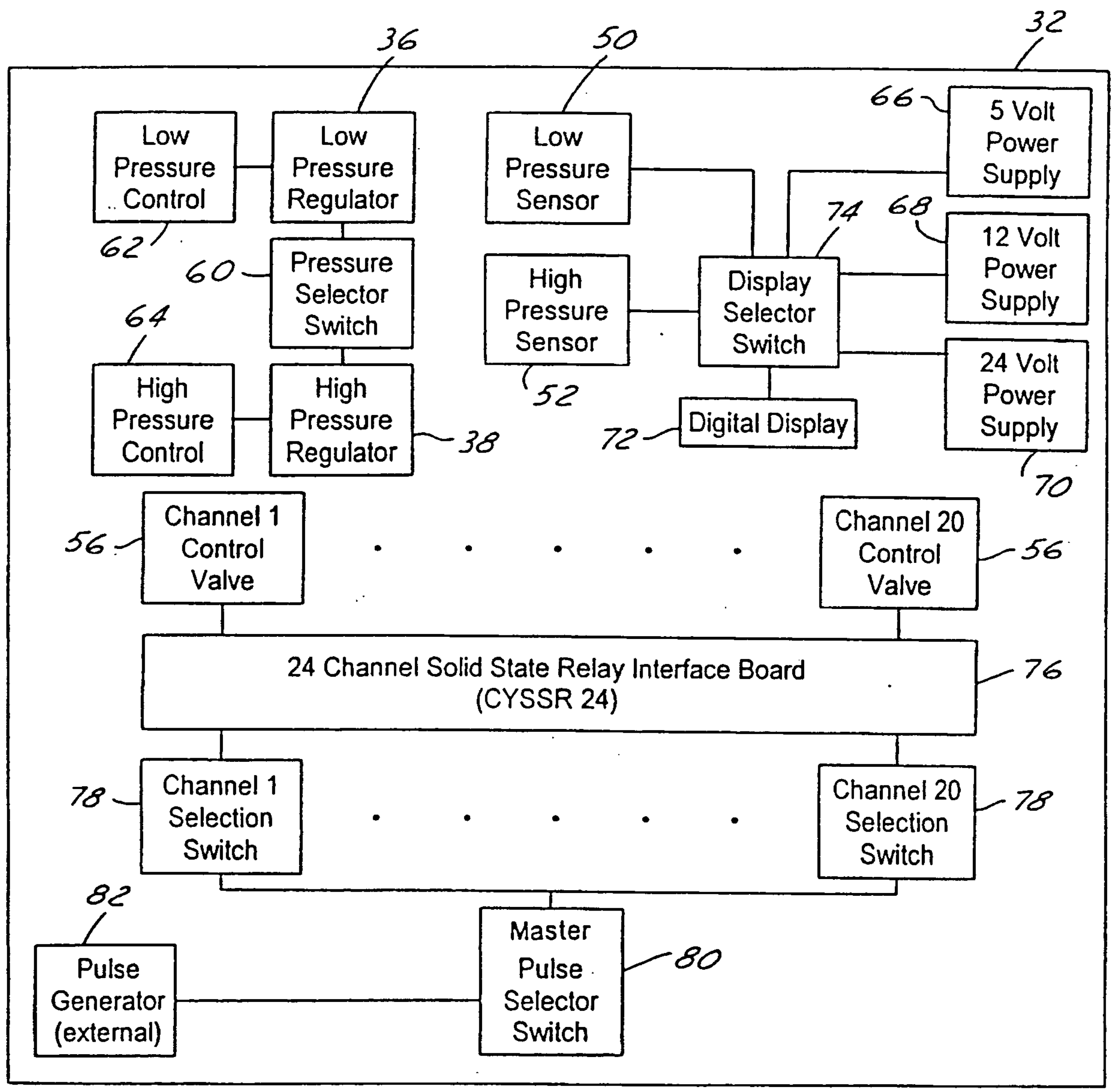


FIG. 3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50
32
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Low Pressure Control
Low Pressure Regulator
Low Pressure Sensor
5 Volt Power Supply
62
74
68
60
Pressure Selector Switch
High Pressure Sensor
Display Selector Switch
12 Volt Power Supply
64
High Pressure Control
High Pressure Regulator
38
52
72
Digital Display
24 Volt Power Supply
70
56
Channel 1 Control Valve
Channel 20 Control Valve
56
24 Channel Solid State Relay Interface Board
(CYSSR 24)
76
78
Channel 1 Selection Switch
Channel 20 Selection Switch
78
82
Pulse Generator (external)
Master Pulse Selector Switch
80

FIG. 4

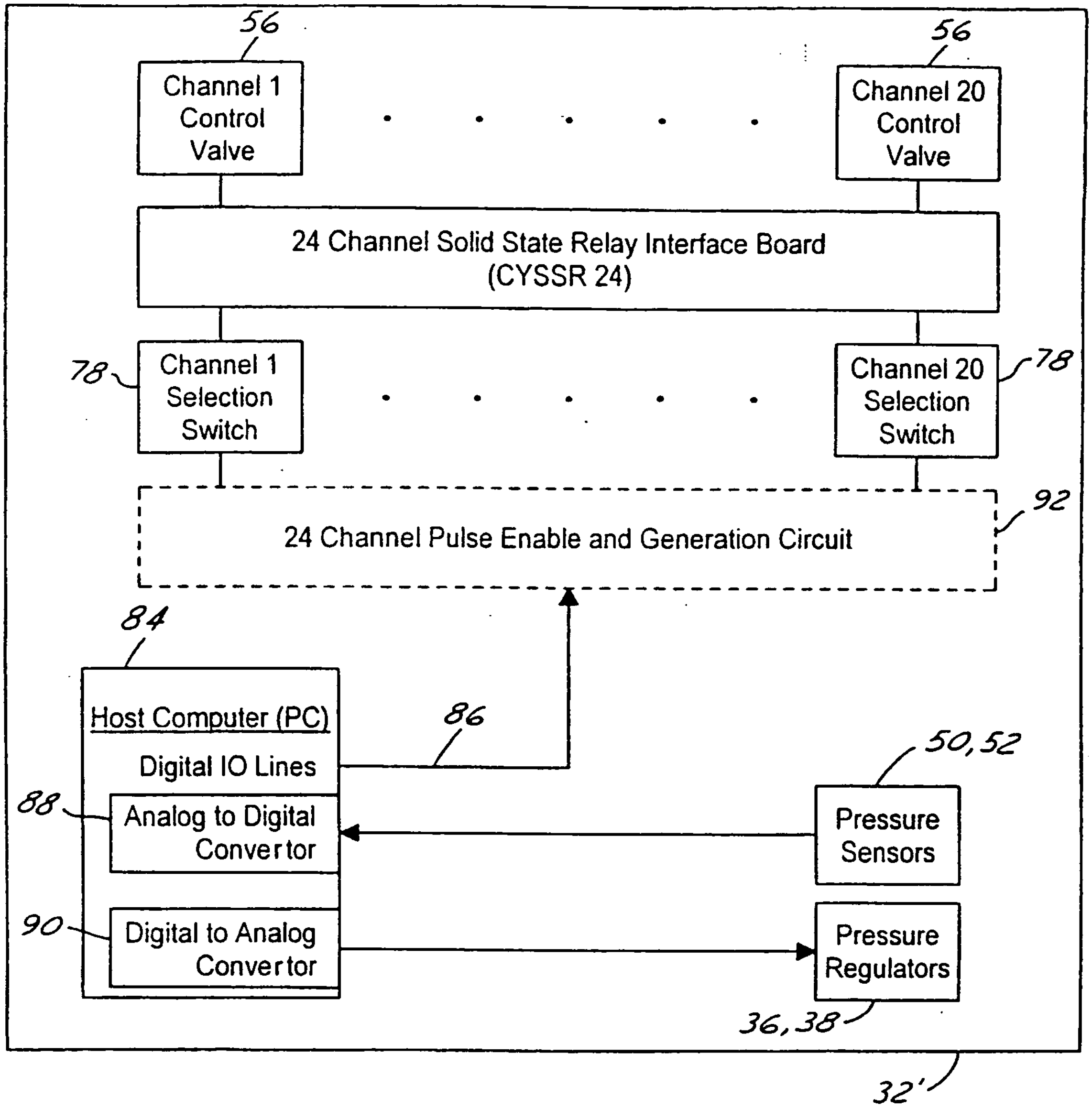
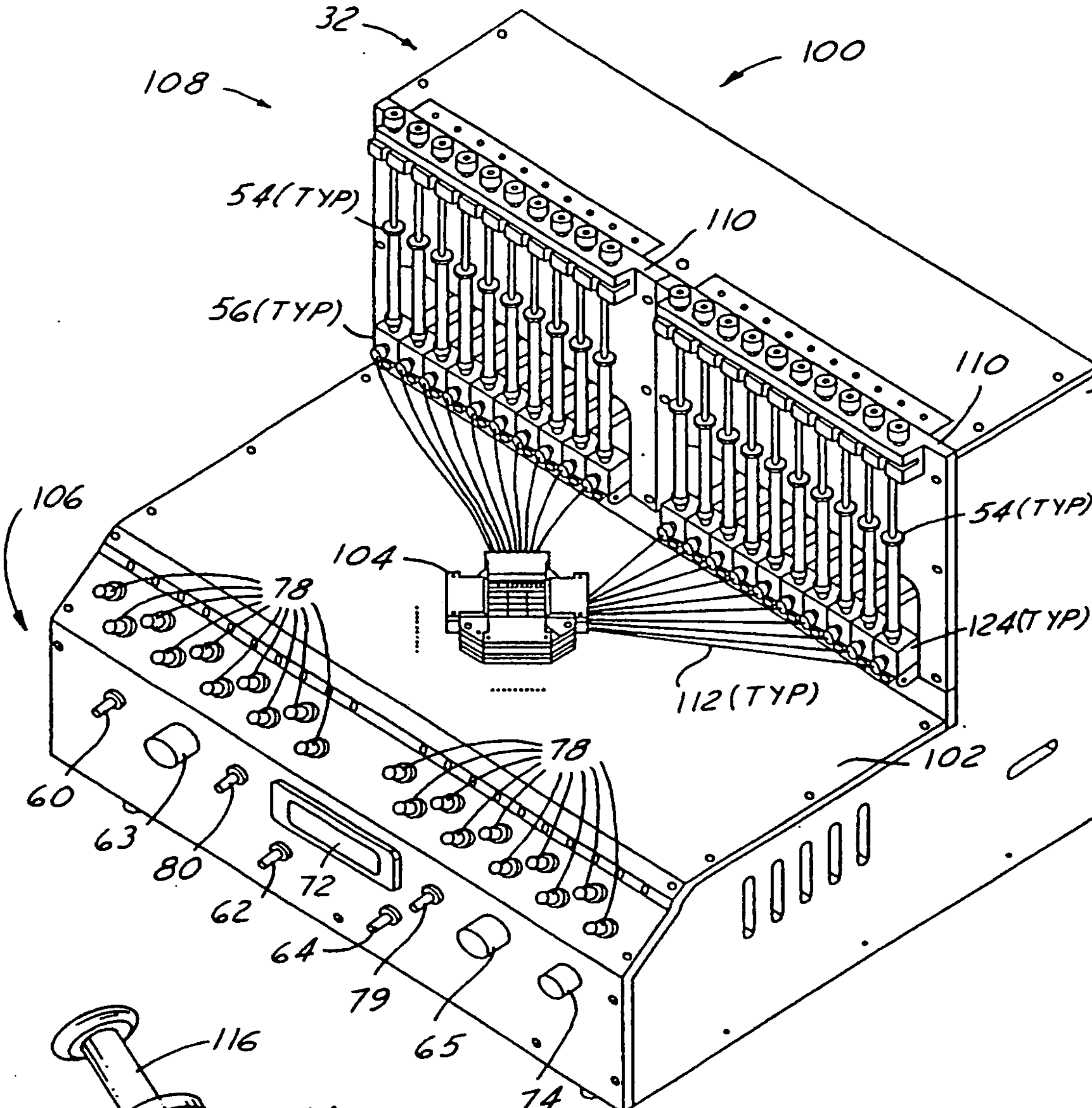

56
Channel 1 Control Valve
56
Channel 20 Control Valve
24 Channel Solid State Relay Interface Board (CYSSR 24)
78
Channel 1 Selection Switch
Channel 20 Selection Switch
78
92
24 Channel Pulse Enable and Generation Circuit
84
Host Computer (PC)
Digital IO Lines
86
50, 52
88
Analog to Digital Convertor
Pressure Sensors
90
Digital to Analog Convertor
Pressure Regulators
36, 38
32'

FIG. 5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100
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54(TYP)
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56(TYP)
108
110
106
54(TYP)
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124(TYP)
112(TYP)
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102
60
63
80
72
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64
79
65
74

FIG.6

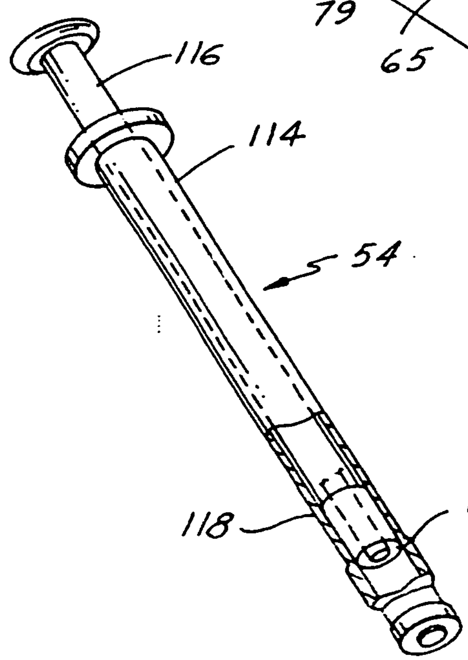
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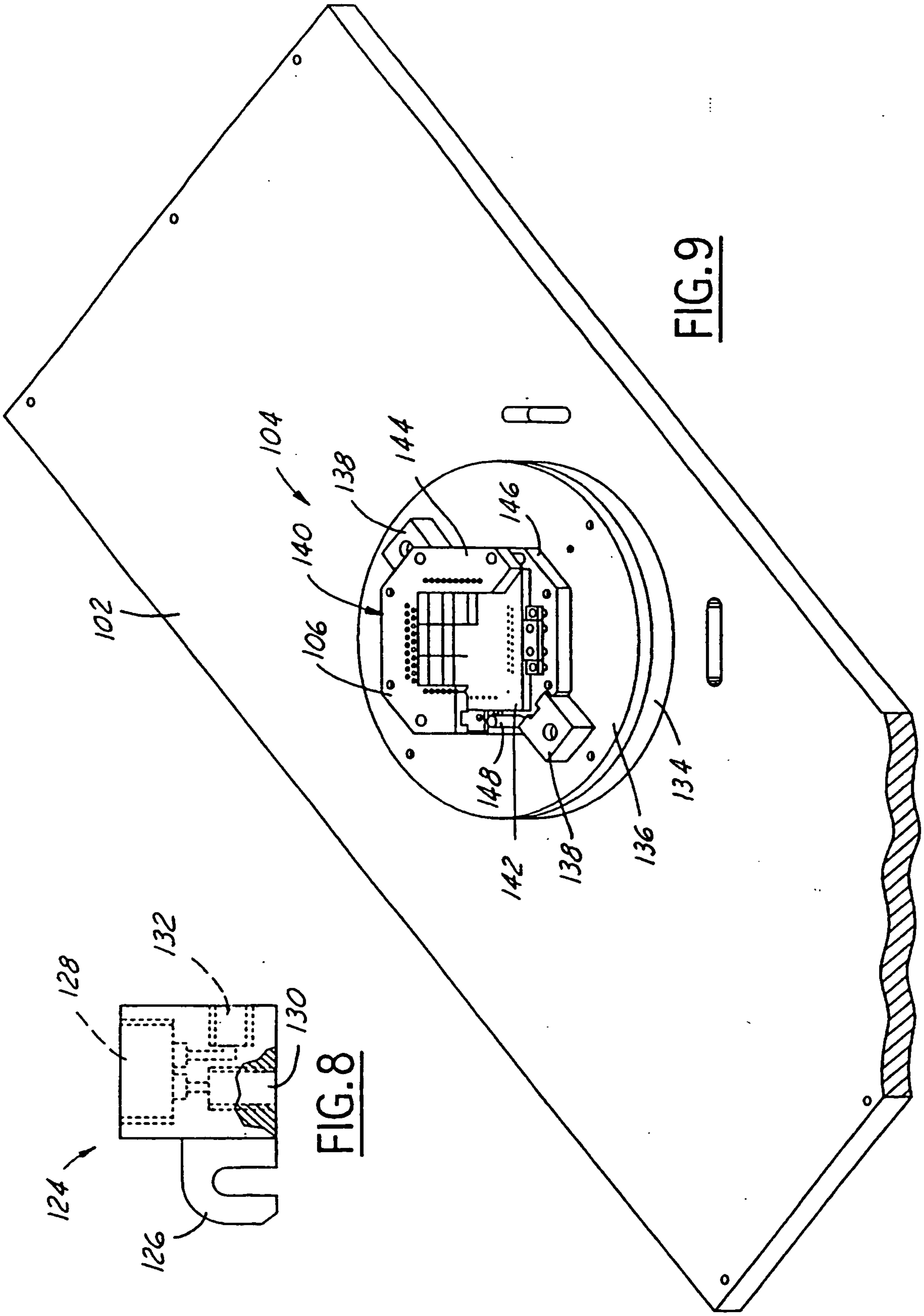
FIG.7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134

FIG.9

128
132
130
124
126

FIG.8

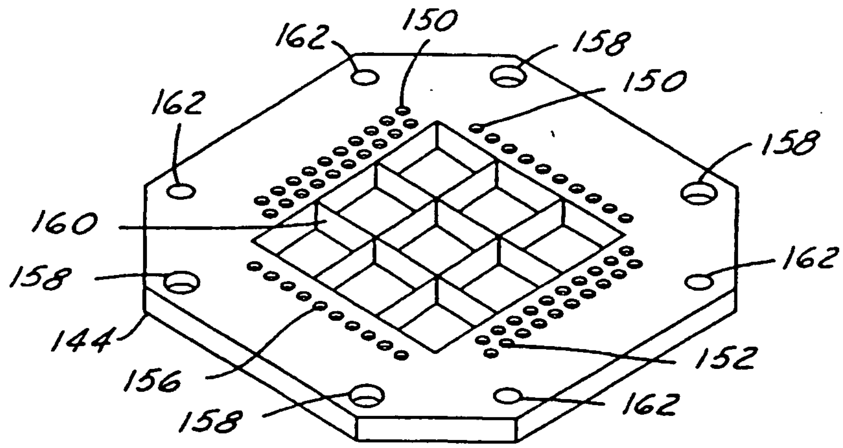


FIG. 10

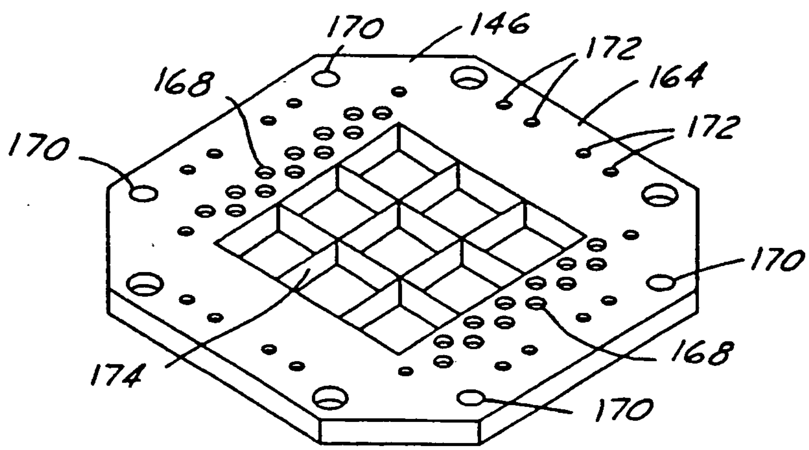


FIG. 11A

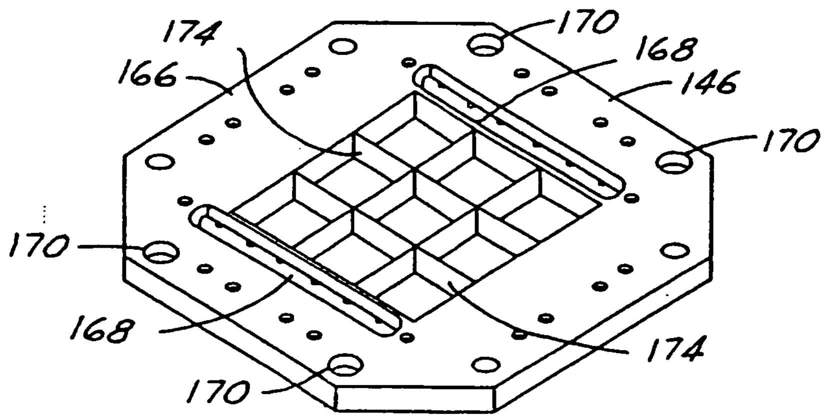
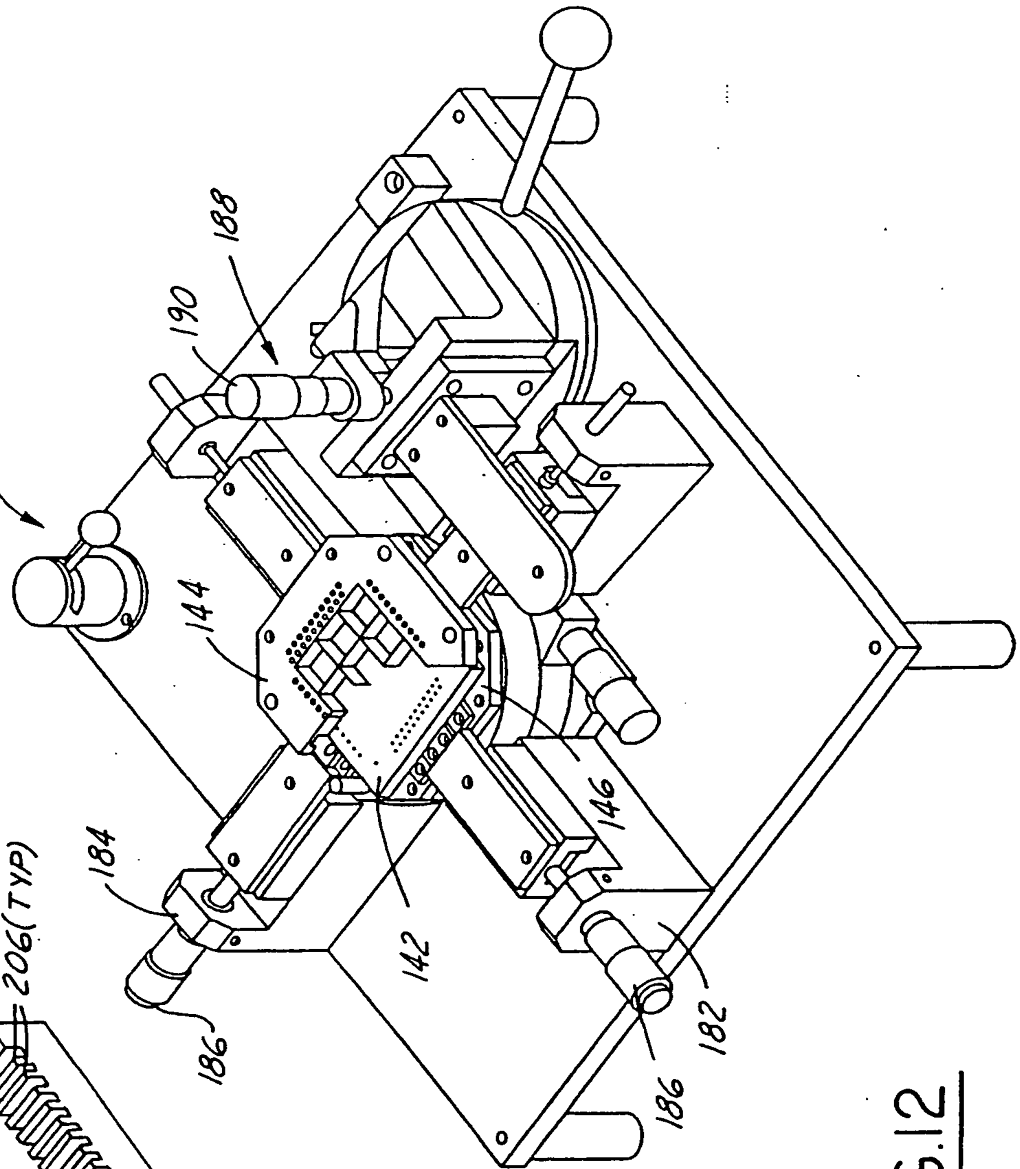


FIG. 11B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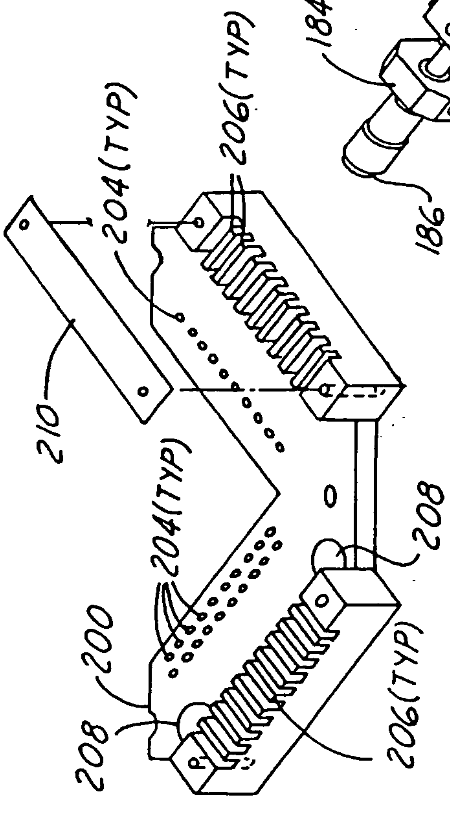
182
186

FIG.12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204(TYP)
206(TYP)
204(TYP)
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208
206(TYP)

FIG.13

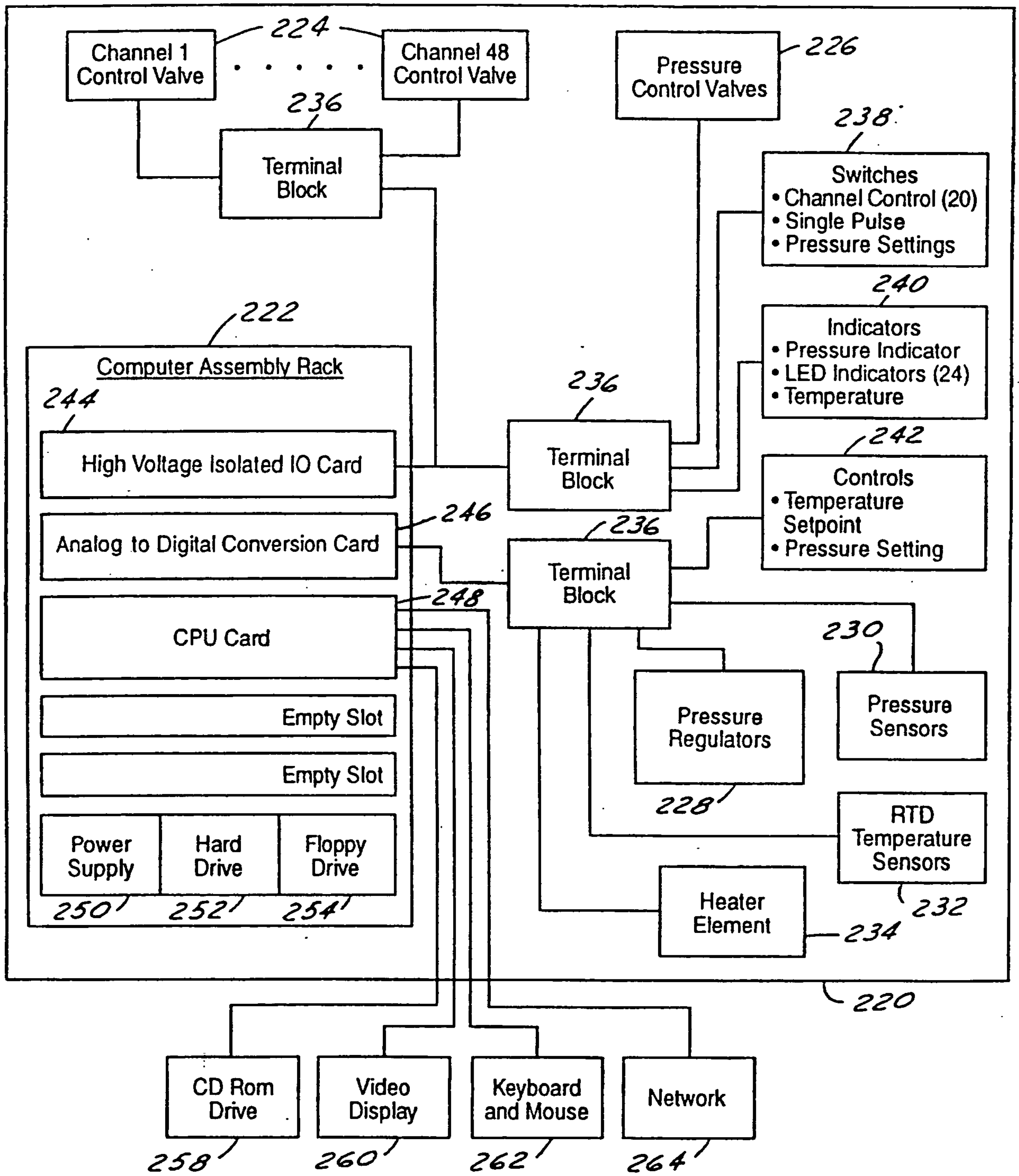
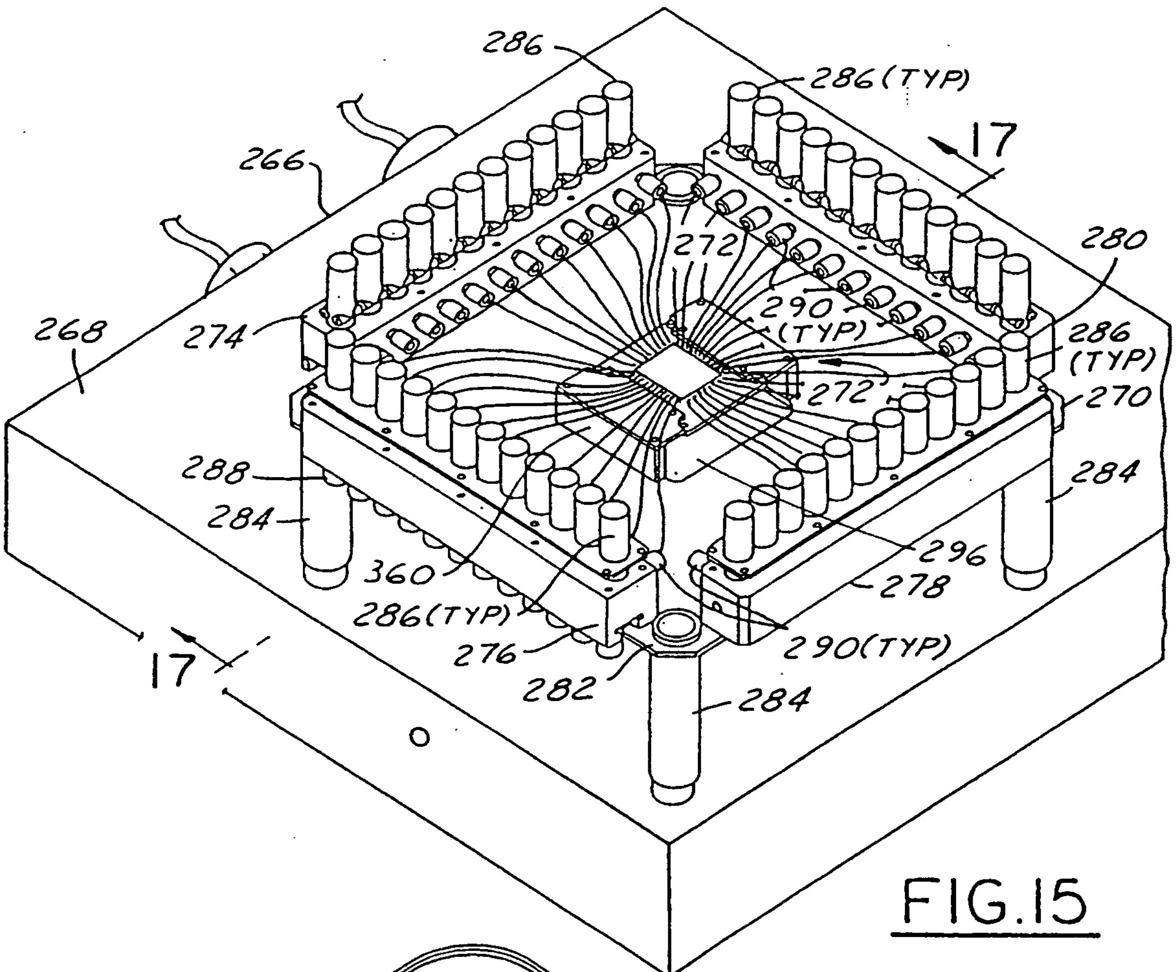

Channel 1 Control Valve
224
Channel 48 Control Valve
Pressure Control Valves
226
236
Terminal Block
238
Switches
• Channel Control (20)
• Single Pulse
• Pressure Settings
240
Indicators
• Pressure Indicator
• LED Indicators (24)
• Temperature
222
Computer Assembly Rack
244
High Voltage Isolated IO Card
236
Terminal Block
242
Controls
• Temperature Setpoint
• Pressure Setting
246
Analog to Digital Conversion Card
236
Terminal Block
248
CPU Card
230
Empty Slot
Empty Slot
Pressure Regulators
Pressure Sensors
228
RTD Temperature Sensors
Power Supply
Hard Drive
Floppy Drive
250
252
254
Heater Element
232
234
220
CD Rom Drive
Video Display
Keyboard and Mouse
Network
258
260
262
264

FIG.14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286(TYP)
17
266
272
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290
(TYP)
268
274
286
(TYP)
272
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360
278
286(TYP)
276
290(TYP)
17
282
284

FIG.15

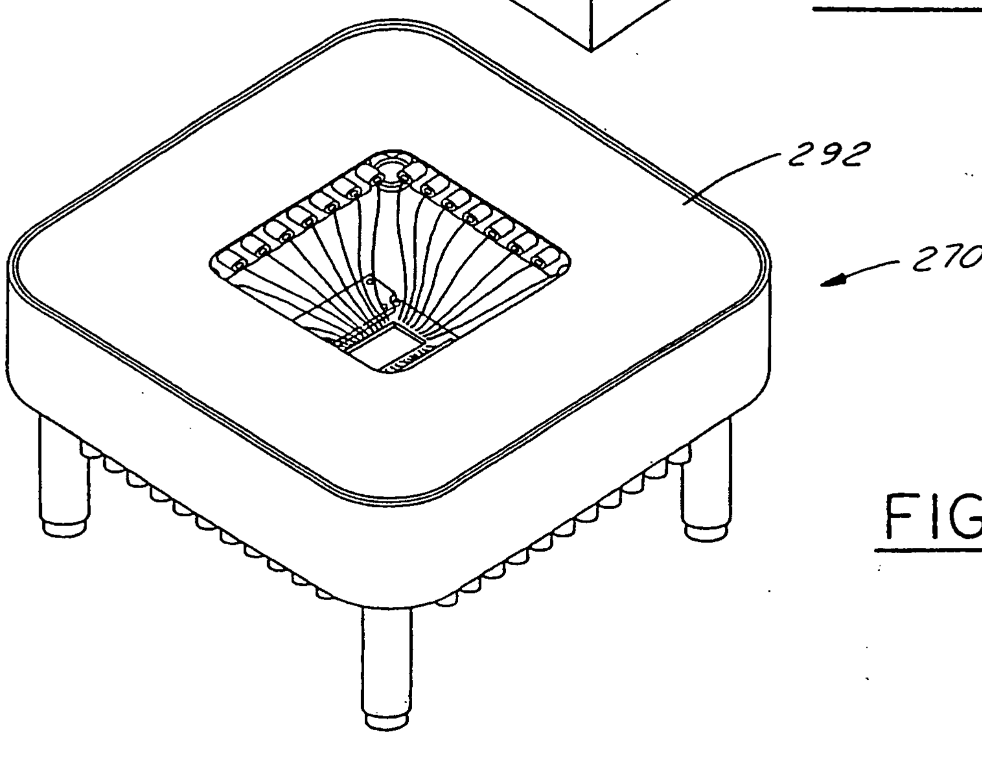
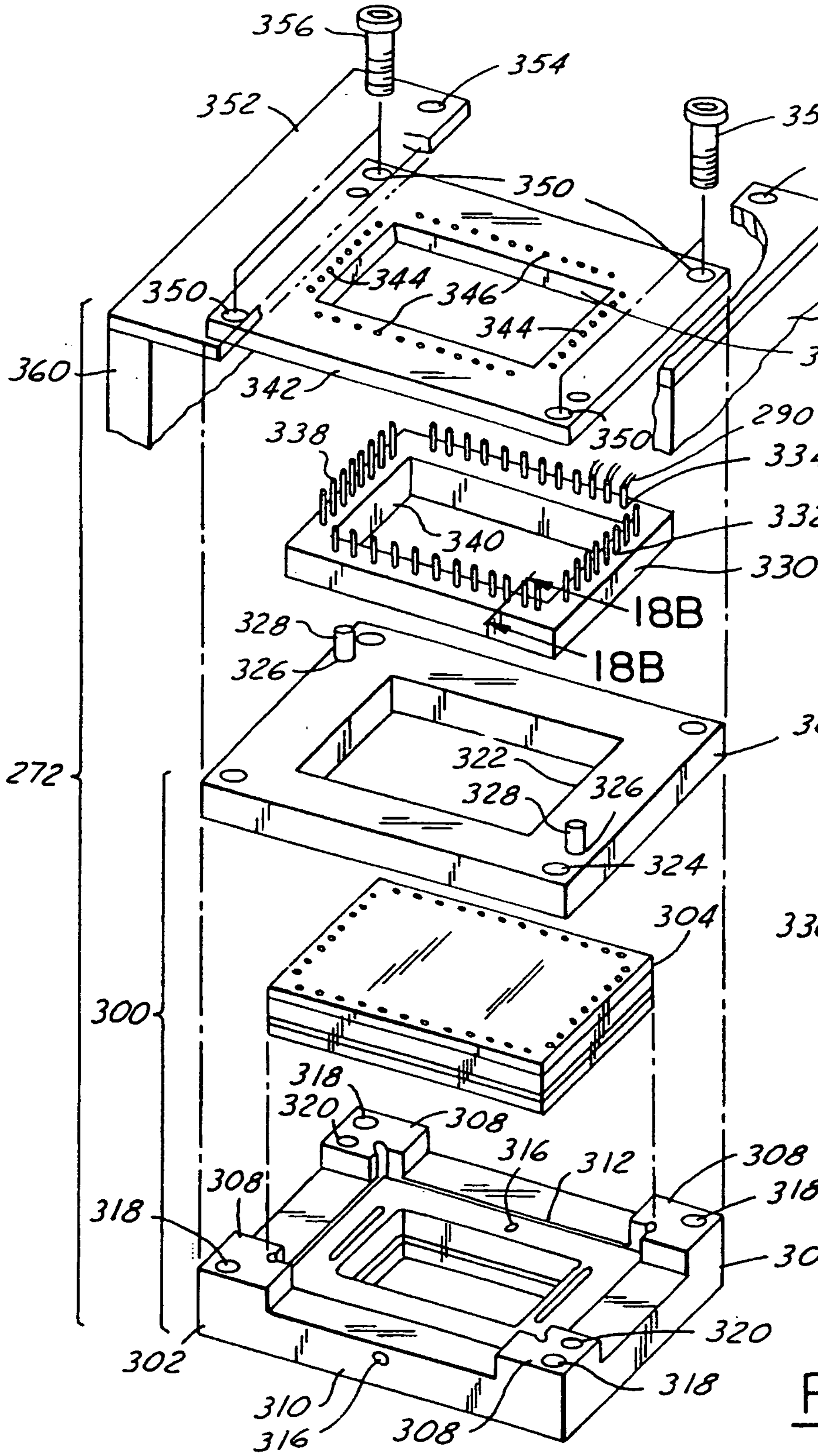

292
270

FIG.16



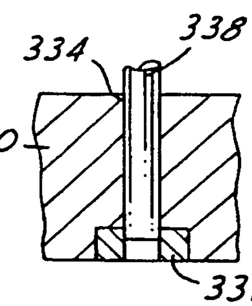


FIG.18B

FIG.18A

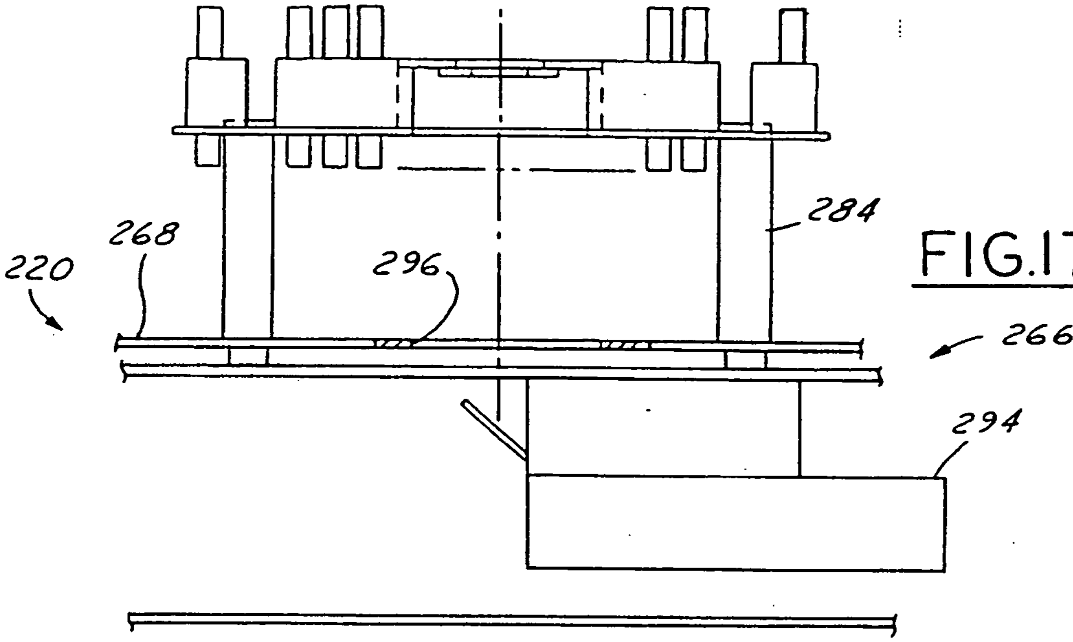
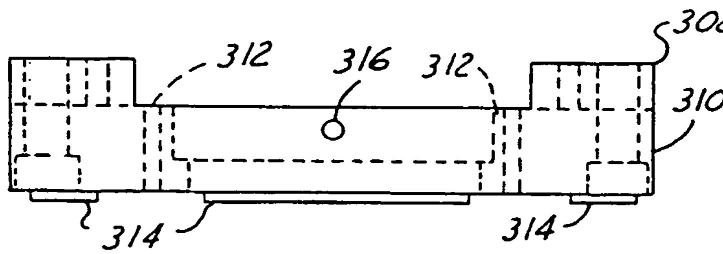


FIG.17

FIG.19



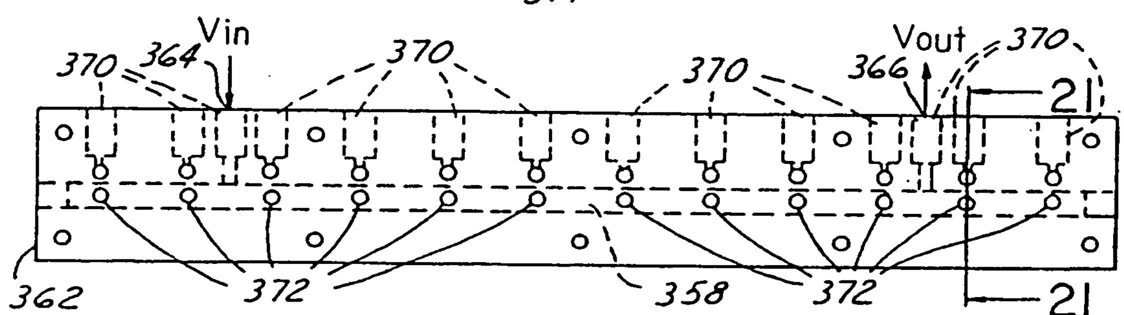


FIG.20

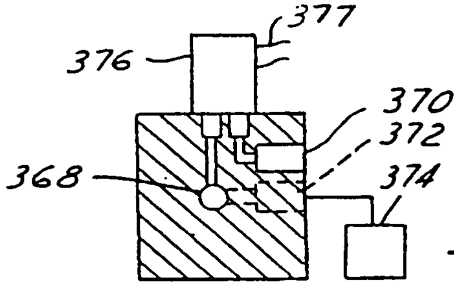


FIG.21

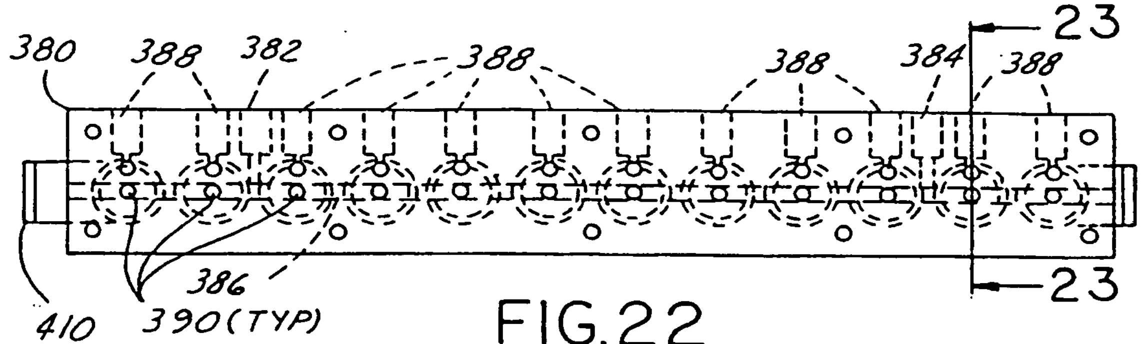


FIG.22

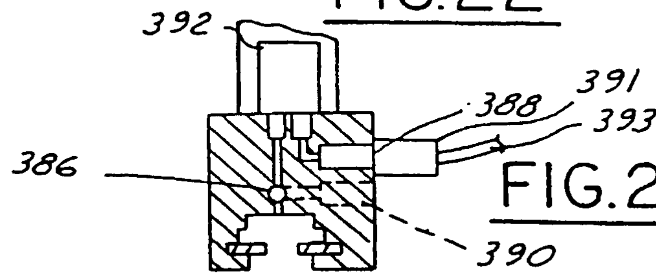


FIG.23

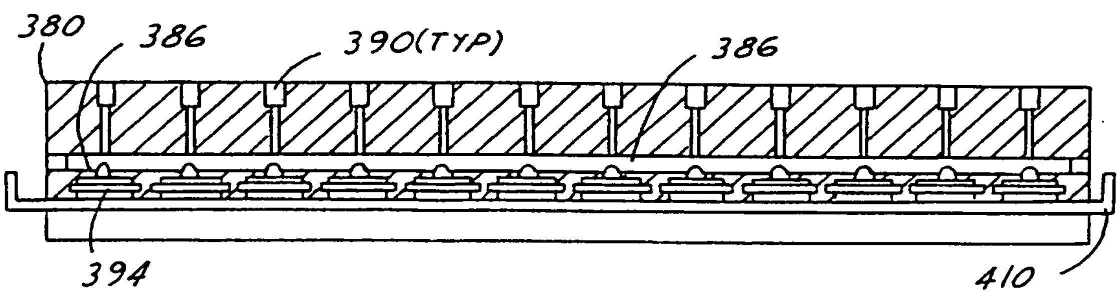


FIG.24

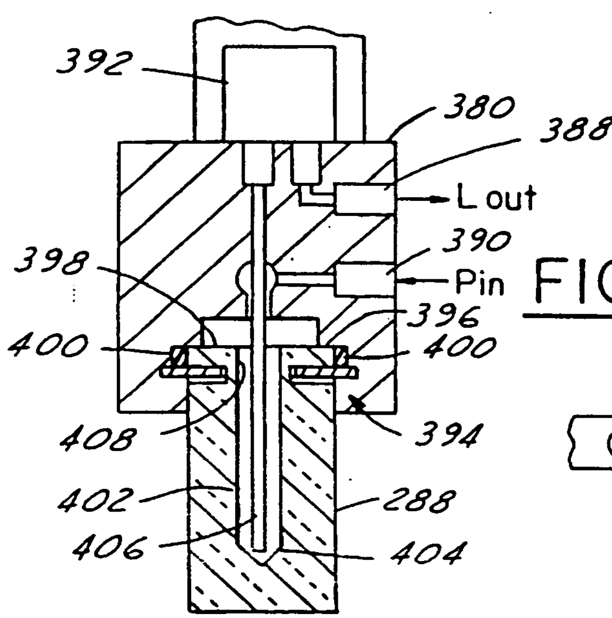


FIG.25

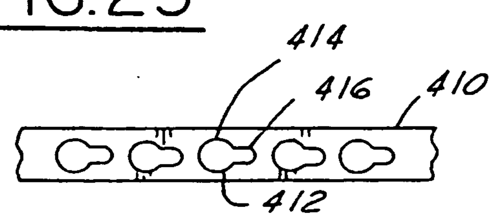


FIG.26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/16886

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :B01L 9/00
US CL :422/104, 99
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 422/99-104; 436/174, 180; 73/863, 863.31, 863.32, 864, 864.11, 864.34

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST search on: microfluidic, microwell, microtiter, fluid or liquid dispens$4, manifold, syringe, Caliper.as.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,830,832 A (ARPAGAUS et al) 16 May 1989, Figures 7-8, col. 5, lines 50-68.	1,3,8,10N
Y	US 5,104,621 A (PFOST et al) 14 April 1992, Figures 1, 11A, columns 9 and 21-22 .	1,3,8,10,24,29
Y	US 5,660,792 A (KOIKE) 26 August 1997, Figures 1 and 5, column 3 and 5.	1,3,8,10,11-14,18,19,21-23,25,26,31
Y, P	US 5,976,470 A (MAIEFSKI et al) 02 November 1999, Figures 1 and 4, columns 7, 8, and 10.	1,3,8,10,18-21
Y, P	US 6,033,911 A (SCHULTZ et al) 07 March 2000, Figure 1, columns 4 and 5.	1,8,9,11,12,18,19,21-23,31

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 SEPTEMBER 2000	13 OCT 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer DWAYNE K. HANDY Telephone No. (703) 308-0661

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	US 6,045,755 A (LEBL et al) 04 April 2000, Figures 1, 15, and 17, columns 27-29.	1,3,8,9,10,11,18,19,21-23,44
A	US 5,873,394 A (MELTZER) 23 February 1999, entire document.	
A	US 5,443,791 A (CATHCART et al) 22 August 1995, entire document.	